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VMAT2 inhibitors for the treatment of tardive dyskinesia: a narrative review

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Review

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Abstract

Two vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, are approved for the treatment of tardive dyskinesia (TD), a persistent and potentially disabling movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents. Since their initial approval in 2017, new formulations and doses for both medications have become available, including a sprinkle capsule for valbenazine and a once-daily tablet for deutetrabenazine. In light of these new therapeutic options, a comprehensive scoping review was conducted to consolidate the current knowledge about these medications. Both valbenazine and deutetrabenazine are safe and effective in treating TD. However, as they are different drugs, one objective of this review is to describe their pharmacology and pharmacokinetics. Another objective is to summarize the similarities and differences as to how these medications are prescribed, specifically in terms of their warnings and precautions, their use in special populations, and recommendations for dosing when taken with concomitant medications. Results from double-blind, placebo-controlled clinical trials are presented, along with post hoc analyses that provide benchmarks for clinical relevance (eg, effect size, number needed to treat, minimal clinically important difference). As most patients with TD will require ongoing treatment, findings from long-term studies provide evidence for the safety and effectiveness of these medications.

Introduction

Two vesicular monoamine transporter 2 (VMAT2) inhibitors, valbenazine and deutetrabenazine, are approved by the U.S. Food and Drug Administration (FDA) for the treatment of tardive dyskinesia (TD) and chorea associated with Huntington's disease (HD).[1,2]

TD is a hyperkinetic movement disorder that is associated with the use of antipsychotics or other dopamine receptor blocking agents (DRBAs). VMATs are transporters located in presynaptic neurons that are involved in packaging and releasing dopamine and other monoamines into the synaptic cleft.[3–5] Two VMAT subtypes have been characterized: VMAT1, expressed in peripheral neuroendocrine cells and sympathetic ganglia, and VMAT2, expressed primarily in the central nervous system.[6] Medications that inhibit VMAT2 reduce the availability of dopamine and other monoamines. In the motor striatum, inhibition of VMAT2 may counteract the dopamine hyperactivity that is thought to be associated with hyperkinetic movement disorders.[3,7,8]

Randomized, double-blind, placebo-controlled (DBPC) clinical trials established the efficacy and safety of these medications for the treatment of TD,[9–14] with supporting evidence from subsequent long-term studies.[9,12,15–19] Both valbenazine and deutetrabenazine showed statistically significant reductions in the motor symptoms of TD, as determined using the Abnormal Involuntary Movement Scale (AIMS[20]) along with global improvements as assessed by study investigators (Clinical Global Impression of Change [CGIC],[21] also referred to as Clinical Global Impression of Change for Tardive Dyskinesia [CGI-TD]) and study participants (Patient Global Impression of Change [PGIC][21]).

Prior to the approval of valbenazine and deutetrabenazine for TD, treatment options were limited and their evidence was generally weak or insufficient.[22] The use of valbenazine and deutetrabenazine for TD is supported by current guidelines from the American Psychiatric Association (APA) and a systematic review of clinical studies that updates evidence-based recommendations for TD following publication of the American Academy of Neurology guidelines in 2013.[23,24] The evidence for tetrabenazine, an older VMAT2 inhibitor approved for HD chorea,[25] is limited by the lack of large, well-controlled clinical trials in TD and safety/tolerability concerns.[24,26,27]

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The development of valbenazine and deutetrabenazine has continued to progress with recently approved additional formulations and doses for both drugs—a capsule containing granules for sprinkling on soft foods for valbenazine and an extended release tablet for deutetrabenazine.[1,2] All approved formulations are safe and effective for TD, but it is important to note that valbenazine and deutetrabenazine are different drugs when making treatment decisions for individual patients. To help elucidate these differences, this article consolidates the pharmacologic, pharmacokinetic, and clinical data for each drug in a single, comprehensive review. Key points are summarized in Table 1, with additional details provided in the supplementary materials.

Characteristics of VMAT2 inhibitors

Pharmacology

Understanding the pharmacology of valbenazine and deutetrabenazine requires some knowledge of tetrabenazine pharmacology and metabolism (Figure 1). Tetrabenazine is a racemic mixture of 2 enantiomers that are reduced to form 4 isomeric dihydrotetrabenazine (HTBZ) metabolites: [+]-α-HTBZ, [+]-β-HTBZ, [−]-α-HTBZ, and [−]-β-HTBZ. Of these 4 metabolites, [+]-α-HTBZ has the highest affinity for VMAT2, followed by [+]-β-HTBZ.[28–30] The [−]-α-HTBZ and [−]-β-HTBZ isomers have negligible affinity for VMAT2, but they (and to a lesser extent [+]-β-HTBZ) demonstrate appreciable affinity for various dopamine, serotonin, and adrenergic receptor subtypes. The use of tetrabenazine is limited by its short half-life and that of its active metabolites, as well as its side effect profile.

Once [+]-α-HTBZ was identified as having the highest affinity and selectivity for VMAT2, valbenazine was created to be a potent, selective, and longer lasting VMAT2 inhibitor by adding a valine ester to [+]-α-HTBZ.[3] This increased the half-life of the active moiety and facilitated once-daily dosing. After oral ingestion of valbenazine, [+]-α-HTBZ metabolite is formed via hydrolysis of the valine ester and is then further metabolized by CYP2D6; no other HTBZ metabolite is formed. Valbenazine also undergoes oxidative metabolism, primarily via CYP3A4/5 enzymes, to form minor metabolites.[29] Valbenazine and its major

Table 1. Valbenazine and deutetrabenazine for tardive dyskinesia

	Valbenazine	Deutetrabenazine
Chemistry	• Valine ester of [+]-α-HTBZ[3]	• Deuterated form of tetrabenazine[31]
Pharmacology and pharmacokinetics (see also Figures 1 and 2, and Supplementary Tables S1–S2)	• Hydrolyzes to form [+]-α-HTBZ[29,30] • Undergoes oxidative metabolism to form mono-oxidized valbenazine (NBI–136110)[29] • VBZ and [+]-α-HTBZ have strong affinity for VMAT2[29,30] • Quickly absorbed and slowly eliminated, allowing for once-daily dosing with both capsules (INGREZZA, INGREZZA Sprinkle)[1]	• Metabolizes into 4 deuterated HTBZ isomers[30] • [−]-α-HTBZ (most abundant) has weak VMAT2 affinity[30] • [+]-β-HTBZ (second most abundant) has strong VMAT2 affinity[30] • Quickly absorbed, with half-life allowing for twice-daily tablet (AUSTEDO); osmotic pump technology allows for once-daily dosing (AUSTEDO XR)[2,35]
Dosing considerations and safety (see also Supplementary Tables S3–S5)	• Warnings include somnolence/sedation, QT prolongation, neuroleptic malignant syndrome, parkinsonism, and depression/suicidality (in Huntington's disease) • Use with MAOIs should be avoided; use in patients with VBZ hypersensitivity is contraindicated • Use with strong CYP3A4 inducers is not recommended due to reduced efficacy • Recommended dosage is 40 mg once-daily for patients taking a strong CYP3A4 inhibitor or strong CYP2D6 inhibitor	• Warnings include somnolence/sedation, QT prolongation, neuroleptic malignant syndrome, akathisia, agitation, restlessness, parkinsonism, and depression/suicidality (in Huntington's disease) • Use with reserpine, MAOIs, and other VMAT2 inhibitors is contraindicated • Use with hepatic impairment is contraindicated • No dosing recommendations for patients taking a CYP3A4 inducer or inhibitor are provided • Maximum recommended dosage is 36 mg/day for patients taking a strong CYP2D6 inhibitor
Clinical trials[a] (see also Supplementary Tables S6–S8)	• 6-wk trials DBPC trials: KINECT,[9] KINECT 2,[10] KINECT 3,[11] J-KINECT[12] • Long-term studies: KINECT Extension (12 wks),[9] KINECT 3 Extension (48 wks),[15] KINECT 4 (48 wks),[16] J-KINECT Extension (48 wks),[12] Study 1506 ([72-wk rollover study])[17]	• 12-wk DBPC trials: ARM-TD[13] and AIM-TD[14] • Long-term study: RIM-TD (145 wks)[18,19]
DBPC trial data: effects on TD (see also Figure 3 and Table 2)	• Significant mean improvement in AIMS total score at 6 wks for both doses (40 and 80 mg) vs. PBO: LSMD (40 mg, −1.8 [nominal $p = 0.002$]; 80 mg, −3.1 [$p < 0.001$])[b]	• Significant improvement in AIMS total score at 12 wks for 2 of 3 doses (24 and 36 mg) vs. PBO: LSMD (24 mg, −1.8 [$p = 0.003$]; 36 mg, −1.9 [$p = 0.001$])
Long-term study data: effects on TD (see also Figures 3 and 4)	• >10-point improvement in AIMS total score after 48 wks of OL treatment (40 mg, −10.2; 80 mg, −11.0), with some loss of effect after 4-wk washout[16] • ~90% of participants met AIMS ≥50%, CGI-TD score ≤2, and PGIC score ≤2 response thresholds at 48 wks[16]	• 6.6-point improvement in AIMS total score after 145 wks of OL treatment (mean dose, 39.4 mg)[19] • 73% and 63% of participants met the response threshold (score ≤2) for CGIC and PGIC at 145 wks[19]
Subgroup analyses (see cited references)	• By baseline psychiatric diagnosis: schizophrenia/schizoaffective disorders, mood disorders[49,50] • By age: <55 and ≥55 years[46] • By age: <65 and ≥65 years[47,48]	• By baseline psychiatric diagnosis: mood disorders and psychotic disorders[52] • By age: <55 and ≥55 years[51] • By baseline DRBA use[52]

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; CGIC, Clinical Global Impression of Change; DBPC, double-blind placebo-controlled; dTBZ, deutetrabenazine; DRBA, dopamine receptor blocking agent; HTBZ, dihydrotetrabenazine; LSMD, least squares mean difference; MAOI, monoamine oxidase inhibitor; OL, open label; PBO, placebo; PGIC, Patient Global Impression of Change; TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter 2; wk, week.
[a]Study 1506 for valbenazine was terminated when the medication became commercially available, and the last study visit reached was Week 60.
[b]LSMDs are from data on file.

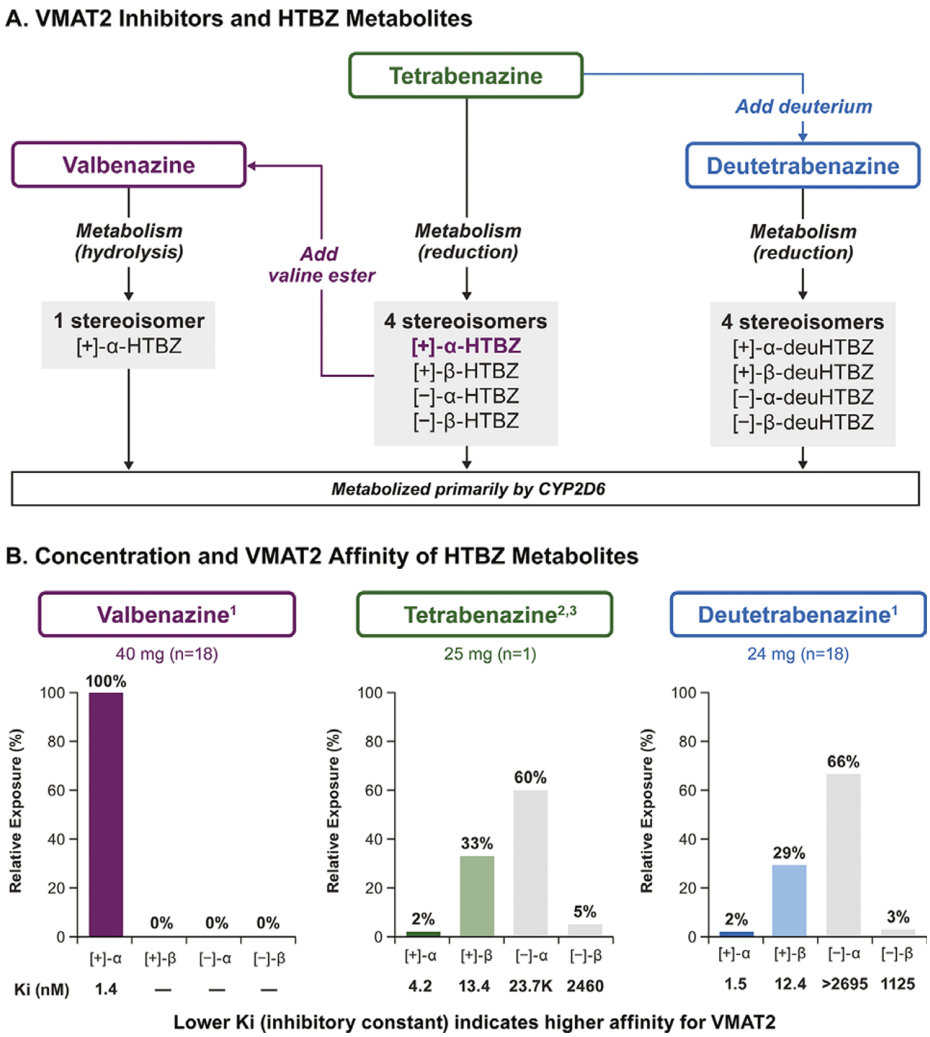

Figure 1. Pharmacology of VMAT2 inhibitors. (A) The structural relationships between tetrabenazine, valbenazine, and deutetrabenazine are presented. Valbenazine is the valine ester of [+]-α-HTBZ, the tetrabenazine metabolite with the highest affinity for VMAT2. Valbenazine undergoes hydrolysis to form only one HTBZ metabolite ([+]-α-HTBZ). Deutetrabenazine is the deuterated form of tetrabenazine. Both tetrabenazine and deutetrabenazine are racemic mixtures and each are reduced to four HTBZ metabolites. (B) Concentrations and affinities of HTBZ metabolites are presented for the three VMAT2 inhibitors. For valbenazine, the only circulating metabolite is [+]-α-HTBZ (purple bar), which has very strong affinity for VMAT2, as indicated by the low inhibitory constant (K_i=1.4 nM). Tetrabenazine and deutetrabenazine have similar profiles, with >60% of circulating metabolizes composed of [-]-α-HTBZ/deuHTBZ and [-]-β-HTBZ/deuHTBZ (light gray bars), which have negligible affinity for VMAT2. For both drugs, the most abundant metabolite with affinity for VMAT2 is [+]-β-HTBZ/deuHTBZ.
Abbreviations: deuHTBZ, deuterated form of HTBZ metabolite; HTBZ, dihydrotetrabenazine; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.
References: [1] Brar et al., *Clin Pharmacol Drug Dev* 2023(4);12:447–56. [2] Skor et al., *Drugs R D* 2017;17(3):449–59. [3] Yao et al., *Eur J Chem* 2011;46(5):1841–8.

metabolite have affinity for VMAT2, with [+]-α-HTBZ having the strongest affinity.

Deutetrabenazine, a deuterated form of tetrabenazine, is the first deuterated drug to receive regulatory approval in the United States.[31,32] Like tetrabenazine, deutetrabenazine is a racemic mixture that forms 4 deuterated HTBZ (deuHTBZ) isomers that are further metabolized by CYP2D6, with contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites. The most prevalent metabolite is [−]-α-deuHTBZ, which has negligible affinity for VMAT2 and varying affinity for off-target receptors.[30] The major active metabolites at VMAT2 for tetrabenazine and deutetrabenazine are [+]-β-HTBZ and [+]-β-deuHTBZ, respectively; both have affinity for VMAT2, but less than [+]-α-HTBZ and [+]-α-deuHTBZ, which account for only approximately 2% of their circulating metabolites.

Pharmacokinetics and dosing

Valbenazine and deutetrabenazine were designed to allow less frequent dosing than is required for tetrabenazine (as indicated for HD chorea).[25] However, their pharmacokinetic profiles are different, which affects their dosing.

Valbenazine is rapidly absorbed after oral administration, reaching a maximum plasma concentration within 1 hour (Supplementary Table S1).[1] Its primary active metabolite, [+]-α-HTBZ, reaches maximum concentration in 4–8 hours. The half-lives of valbenazine and [+]-α-HTBZ (15–22 hours[1]) allow once-daily dosing without any sustained release modification.

The valbenazine label includes 3 clinically effective once-daily doses (40, 60, and 80 mg) that can be taken with or without food (Figure 2). Two doses were initially approved (40 and 80 mg), but it became apparent that a third dose (60 mg) could potentially fill

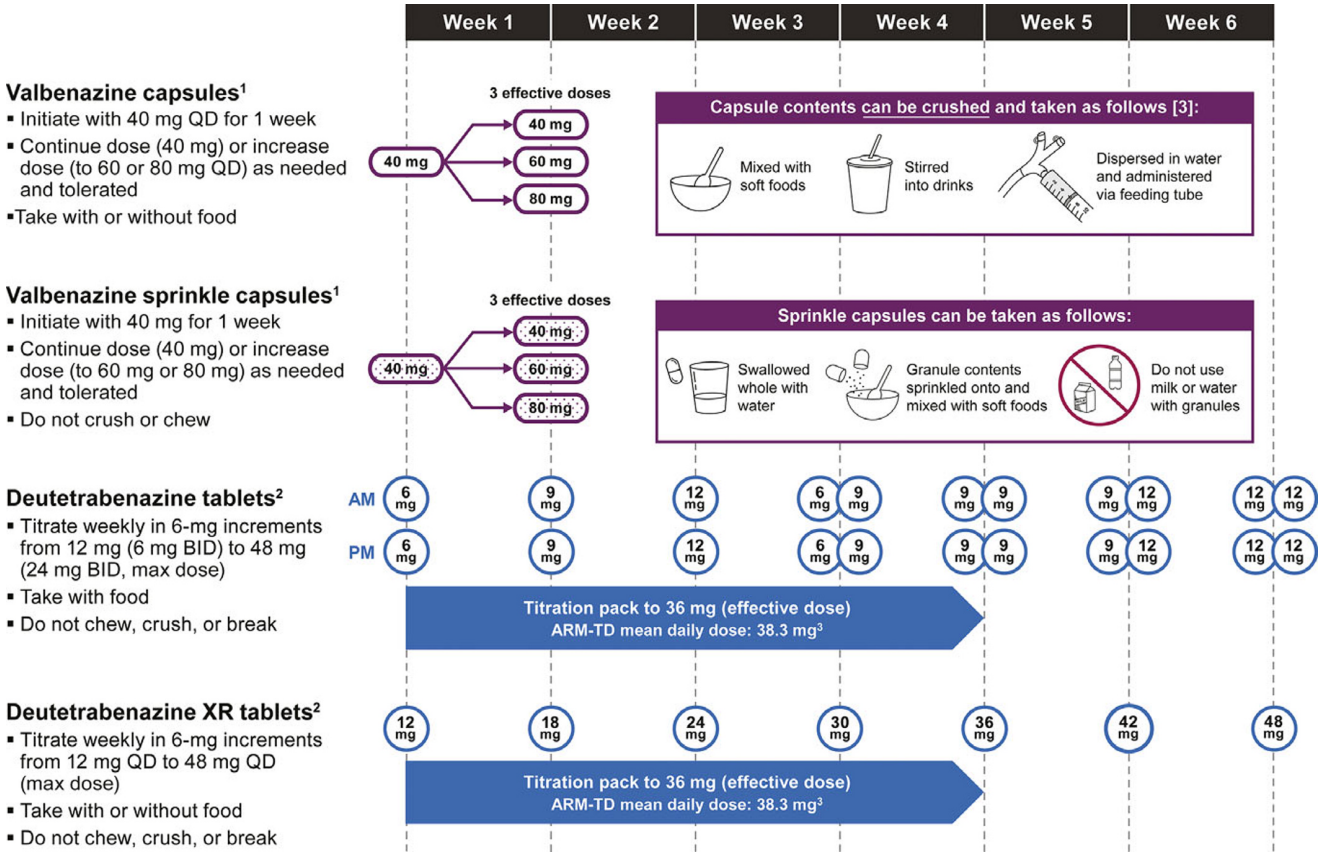

Figure 2. Dosing and administration for valbenazine and deutetrabenazine. Information in this figure reflects prescribing recommendations for TD, as stated in the package inserts for valbenazine (INGREZZA® and INGREZZA® SPRINKLE) and deutetrabenazine (AUSTEDO® and AUSTEDO® XR), along with results from an in vitro study of crushed valbenazine capsule contents (Sajatovic 2023).
Abbreviations: BID, twice-daily; QD, once-daily; TD, tardive dyskinesia; XR, extended-release.
References: [1] Prescribing information for INGREZZA® and INGREZZA® SPRINKLE; February 2025. [2] Prescribing information for AUSTEDO® and AUTEDO® XR; February 2025. [3] Sajatovic et al., *Clin Ther* 2023;45(12):1222–7.

a clinical need. Efficacy for valbenazine 60 mg was established using the FDA's model-informed drug development approach (Supplementary Table S2),[33] and this dose was approved by the FDA in April 2021. A stepwise increase from 40 to 60 to 80 mg is not required but can be used for patients with TD. After taking valbenazine 40 mg for 1 week, patients can continue with 40 mg or switch to either of the higher doses (60 or 80 mg) as warranted by patient clinical status, though the treatment effect size when comparing the randomized groups was greater in magnitude for the 80 mg dose.[34]

The maximum plasma concentrations of deutetrabenazine and its metabolites are reached at approximately 3–4 hours after oral administration (Supplementary Table S1).[2] Its deuterated HTBZ metabolites are primarily metabolized by CYP2D6, with minor contributions from CYP1A2 and CYP3A4/5. The metabolite half-lives range from 9 to 12 hours, allowing for twice-daily dosing with the original tablet formulation, which is also required to be taken with food.

Extended release tablets using passive osmotic diffusion were developed to enable once-daily dosing with deutetrabenazine.[2] In contrast to the twice-daily tablets, the extended release tablets can be taken with or without food. As noted in the phase 1 study that demonstrated acceptable bioequivalence with the original twice-daily tablet (Supplementary Table S2), extended release deutetrabenazine can reduce pill burden and potentially improve medication adherence.[35] The dose titration schedule, however, remains unchanged (Figure 2). Most patients need 4 weeks to reach an effective dose (36 mg), as evidenced in a flexible dose study,[14] though 24 mg, observed to be therapeutic in a fixed dose study,[13] is reached by Day 15. Regardless of formulation or target dose, retitration is needed when stopping deutetrabenazine for ≥1 week.

Alternative routes of administration

Valbenazine sprinkle capsules were developed to address the needs of patients with TD and HD who have difficulties swallowing or do not want to take whole capsules due to motor symptoms, advanced age, or other conditions. The capsules can be opened manually, allowing the granule contents to be sprinkled onto soft foods.[1] An in vitro study established that these granules are compatible with a wide range of soft foods (eg, mashed fruit, mashed potatoes, yogurt, pudding), and a phase 1 study established bioequivalence with the original valbenazine capsule (Supplementary Table S2).[36] Moreover, the compacted powder content of the original capsule has been studied in vitro and met acceptable criteria when crushed and mixed with soft foods or liquids, or dispersed in water for delivery via a gastrostomy tube.[37] Thus, both valbenazine capsules offer options for patients who have difficulty swallowing, fear of choking, or other forms of pill aversion. For these patients, deutetrabenazine might not be an option since the prescribing information advises that tablets are to be swallowed whole, and not chewed, crushed, or split.[2]

Safety

Valbenazine and deutetrabenazine have many similar warnings and contraindications (Supplementary Table S3). The product labels for both medications include boxed warnings about depression and suicidality in patients with HD, a warning for use in patients with prolonged QT intervals (with different language regarding when to assess the QT interval), recommend discontinuation if neuroleptic malignant syndrome occurs, and prohibit concomitant use with monoamine oxidase inhibitors.[1,2]

Somnolence and sedation

Both medications carry a warning about somnolence and sedation, which can affect a patient's ability to drive or operate hazardous or complex machinery.[1,2]

As reported in the prescribing information for valbenazine, the incidence of somnolence (defined as somnolence, fatigue, sedation) was 10.9% versus 4.2% for placebo.[1] In the 6-week KINECT 3 study, the incidences for each of these adverse effects separately were as follows: somnolence (5.3% vs. 3.9% for placebo); fatigue (2.0% vs. 1.3%); sedation (0.7% vs. 0%).[11]

Incidence of somnolence in TD (either alone or pooled with fatigue and/or sedation) is not reported in the product label for deutetrabenazine as the rate did not meet the reporting threshold of at least 2% of patients and greater than placebo.[2] Reported incidences in the 12-week TD trials were as follows: ARM-TD (somnolence, 13.8% vs. 10.2% for placebo; fatigue, 6.9% vs. 8.5%); AIM-TD (somnolence 2% vs. 4% for placebo; fatigue, 3% vs. 1%; sedation, <1% vs. 0%).[13,14]

Parkinsonism and other abnormal movements

Valbenazine and deutetrabenazine both carry a warning about parkinsonism, with deutetrabenazine also carrying a warning for akathisia, agitation, and restlessness.[1,2] For both medications, postmarketing cases of parkinsonism were reported in patients with TD, mostly within the first 2 weeks of starting treatment or increasing the dose. The reported incidence of akathisia/restlessness/agitation was 2–3% for both medications. All patients taking these medications should be monitored for any signs of parkinsonism, akathisia, or other non-TD movements.

Hyperprolactinemia

A dose-related increase in prolactin was observed in the DBPC trials of valbenazine, and the potential for cholestasis is noted.[1] Prolactin was not evaluated in the deutetrabenazine studies, but hyperprolactinemia is included as a warning for deutetrabenazine use based on studies with tetrabenazine. In healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold after administration of tetrabenazine 25 mg.[2]

Dosing considerations

With concomitant medications

The effects of comedications on valbenazine pharmacokinetics were evaluated in phase 1 studies.[38,39] Coadministration of valbenazine with strong CYP3A4 inducers is not recommended, as these drugs may reduce the exposure (and therefore effectiveness) of valbenazine and [+]-α-HTBZ (Supplementary Table S4).[1] There are no prohibitions for taking valbenazine with a strong CYP3A4 inhibitor or strong CYP2D6 inhibitor, and the 40-mg dose is recommended as these drugs may increase the exposure of valbenazine and [+]-α-HTBZ.

Regarding deutetrabenazine, a phase 1 study in healthy individuals was conducted with paroxetine, a strong CYP2D6 inhibitor (Supplementary Table S4). The exposure of α-deuHTBZ and β-deuHTBZ metabolites was found to increase by 1.9- and 6.5-fold, respectively.[2] Therefore, the maximum recommended daily dosage of deutetrabenazine is 36 mg in patients who are taking a strong CYP2D6 inhibitor. In vitro studies showed that at clinically relevant concentrations, deutetrabenazine and its active metabolites did not inhibit or induce CYP3A4 enzymes.[2]

The effects of CYP3A4 inhibitors or inducers on deutetrabenazine pharmacokinetics have not been reported. No dose modification of deutetrabenazine is required in the presence of CYP3A4 inducers or inhibitors.

In specific populations

For both valbenazine and deutetrabenazine, there are limited or no available data for the following: use in pregnant women or breastfeeding infants; effects on milk production or presence in human breast milk; use in pediatric patients (Supplementary Table S5).[1,2]

The effects of hepatic impairment, renal impairment, and poor CYP2D6 metabolism on valbenazine pharmacokinetics were evaluated in phase 1 studies. Based on these study results, dosing recommendations for valbenazine are as follows: dose reduction in patients with moderate or severe hepatic impairment (Child-Pugh score 7–15); no dose adjustment for patients with mild, moderate, or severe renal impairment; dose reduction in CYP2D6 poor metabolizers.[1] Finally, based on available data from TD and HD clinical trials, no dose adjustment is needed in elderly patients.

The effects of hepatic and renal impairment on deutetrabenazine pharmacokinetics have not been clinically evaluated. However, based on findings with tetrabenazine, deutetrabenazine is contraindicated in patients with hepatic impairment. No dosing recommendations are available for patients with renal impairment (Supplementary Table S5). Based on the increased exposure of deutetrabenazine metabolites when coadministered with paroxetine, a strong CYP2D6 inhibitor, a maximum daily dose of 36 mg is recommended for patients who are CYP2D6 poor metabolizers. The TD and HD clinical trials of deutetrabenazine did not include a sufficient number of elderly patients to determine specific dosing recommendations; however, the product label suggests starting with a low dose and increasing doses with caution.

Double-blind placebo-controlled trials

The DBPC trials of valbenazine and deutetrabenazine included dose-escalation studies (Supplementary Table S6)[10,13] and fixed dose studies (Supplementary Table S7)[11,12,14]. The valbenazine studies required moderate or severe TD at screening per central rater judgment and were 6 weeks in duration. The deutetrabenazine studies required an AIMS total score ≥6 at screening and baseline and were 12 weeks in duration to accommodate the 4-week dose titration period. All studies defined their primary endpoint as a change from baseline in AIMS dyskinesia total score (sum of items 1–7), as assessed by blinded central video raters.

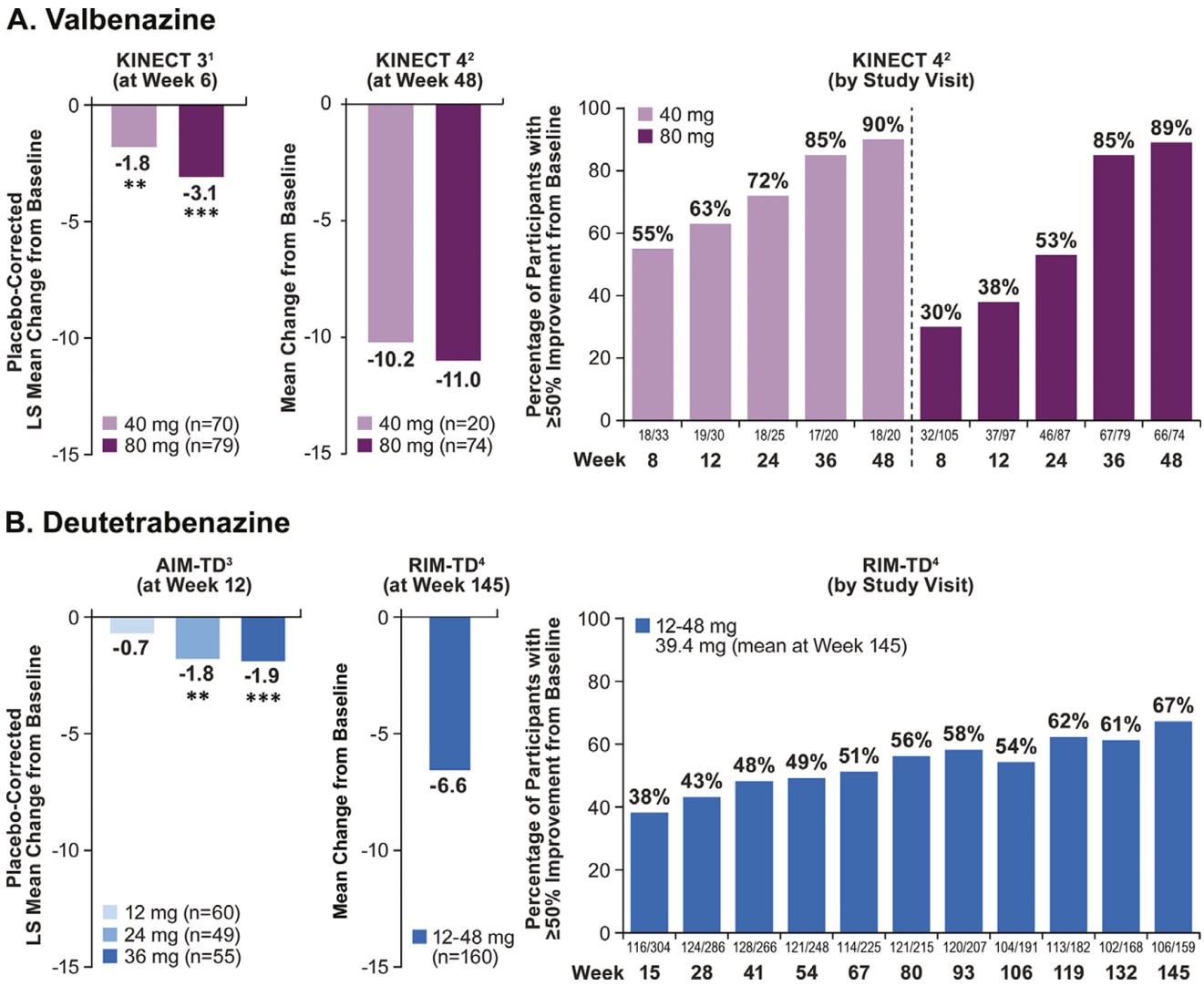

Figure 3. AIMS outcomes in DBPC trials and long-term studies. **p<0.01; ***p<0.001 versus placebo.
The AIMS is a 12-item scale used to evaluate the severity of abnormal movements, and the total score is calculated by summing the item scores from each body region (items 1-7). In phase 3 clinical trials (KINECT 3 and AIM-TD), the AIMS was scored by central video raters who were blinded to treatment assignment and study visit. In open-label studies (KINECT 4 and RIM-TD), AIMS was scored by study investigators. (A) At Week 6 in KINECT 3, placebo-corrected LS mean changes from baseline (i.e., LSMD) were significant for both valbenazine doses (40 and 80 mg, once daily) [data on file]. At Week 48 in KINECT 4, AIMS total score decreased by -10.2 points, and ~90% of participants achieved ≥50% improvement from baseline. (B) At Week 12 in AIM-TD, placebo-corrected LS mean changes from baseline (i.e., LSMD) were significant for two deutetrabenazine doses (18 and 24 mg, twice-daily). At Week 145 in RIM-TD, AIMS total score decreased by 6.6 points, and 67% achieved ≥50% improvement from baseline.
Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BID, twice-daily; LS, least squares; LSMD, least squares mean difference; OL, open-label; TD, tardive dyskinesia.
References: [1] Hauser et al., *Am J Psychiatry* 2017;174(5):476–84. [2] Marder et al., *J Clin Psychopharmacol* 2019;39(6):620–7. [3] Anderson et al., *Lancet Psychiatry* 2017;4(8):595–604. [4] Hauser et al., *Front Neurol* 2022;13:773999.

Concomitant use of antipsychotics and antidepressants was allowed in the DBPC trials of both medications; however, concomitant anticholinergic use was only allowed in the studies of valbenazine.

Valbenazine

Both DPBC trials of valbenazine met their primary endpoint (Supplementary Tables S6 and S7). At Week 6 in KINECT 2, the least squares mean difference (LSMD or "placebo-corrected" difference) for the AIMS total score change from baseline was −2.4 (p = 0.0005), indicating a significantly greater improvement with valbenazine (25–75 mg once-daily) versus placebo.[10]

KINECT 3 (phase 3 study) implemented a fixed sequence testing procedure, with the first step (primary endpoint) defined as statistical significance for valbenazine 80 mg versus placebo for AIMS total score change.[11] This step was met, with LSMDs at Week 6 of −3.1 (p < 0.001) and −1.8 (nominal p = 0.002) for valbenazine 80 and 40 mg, respectively (Figure 3). Both valbenazine dose groups showed a statistically significant improvement in AIMS total score by Week 2: 40 mg (LSMD −1.4, nominal p = 0.031); 80 mg (LSMD −1.6, nominal p = 0.001) (data on file).

Results from J-KINECT (Japanese phase 3 study)[12] were consistent with those from KINECT 3, and its findings supported the approval of valbenazine for TD in Asia. For AIMS total score change from baseline to Week 6, LSMDs indicated statistical

significance for valbenazine 40 mg (−2.2, $p < 0.001$) and 80 mg (−3.6, $p < 0.001$) versus placebo.

Deutetrabenazine

Both DBPC trials of deutetrabenazine met their primary endpoints (Supplementary Tables S6 and S7). At Week 12 in ARM-TD, a significantly greater decrease in AIMS total score was found with deutetrabenazine (6–24 mg BID) versus placebo, with an LSMD of −1.4 ($p = 0.019$).[13]

In AIM-TD (phase 3 study), significant improvements in AIMS total score were found with two deutetrabenazine doses, 12 mg BID (24 mg/day) (LSMD −1.8, $p = 0.003$) and 18 mg BID (36 mg/day) (LSMD −1.9, $p = 0.001$) (Figure 3).[14] Statistically significant improvements on AIMS total score were detected by Week 2 with both doses: 12 mg BID (LSMD −1.4, nominal $p = 0.006$); 18 mg BID (LSMD −1.1, nominal $p = 0.032$).

Post hoc analyses

In clinical trials, change from baseline in AIMS total score demonstrated reductions in TD severity with valbenazine and deutetrabenazine.[10–17,19] In 2016, a panel of TD experts met to discuss the challenges of translating these AIMS results from clinical trials into clinical practice.[13] After reviewing data from the KINECT 3 trial, they proposed several types of post hoc analyses that would help clinicians better understand and communicate the magnitude of treatment effects. Described in detail next, these approaches include Cohen's *d* effect size, number needed to treat (NNT), and minimally clinical important difference or change (MCID for valbenazine, MCIC for deutetrabenazine).

AIMS effect size

Cohen's *d*, which is calculated from the standardized mean difference between 2 groups (eg, active drug and placebo), is typically interpreted using benchmarks of ~0.2 (small effect), ~0.5 (medium effect), and ~0.8 (large effect).[40]

Cohen's *d* effect sizes have been reported based on AIMS total score changes from baseline (Table 2). In KINECT 3, effect sizes at Week 6 for valbenazine 40 mg and 80 mg were 0.5 and 0.9, respectively.[41] In AIM-TD, an effect size of 0.6 was detected at Week 12 for both deutetrabenazine doses (12 and 18 mg BID) that demonstrated statistical significance for AIMS total score improvement.[42]

Number needed to treat

NNT describes how many patients need to receive one intervention versus another (eg, active drug vs. placebo) to expect one additional desired outcome, with a lower NNT indicating a stronger treatment effect versus placebo.[43] In the phase 3 trials of valbenazine and deutetrabenazine, the percentage of participants who reached a response threshold of ≥50% improvement in AIMS total score at the end of DBPC treatment was significantly greater with active drug than with placebo (Table 2). Calculated NNTs versus placebo using these response data for valbenazine were 7 (40 mg) and 4 (80 mg) at Week 6.[34] For deutetrabenazine, a NNT versus placebo

Table 2. Clinical relevance of AIMS clinical trial results

KINECT 3 study results (valbenazine)[11,41]	Corresponding post hoc analysis[41]
LSM CFB in AIMS total at Week 6 • PBO (−0.1); 40 mg (−1.9); 80 mg (−3.2)*	Cohen's *d* effect size at Week 6 • Week 6: 40 mg (0.5); 80 mg (0.9)
LSM CFB in AIMS item scores at Week 6 • Face: PBO (0.1); 40 mg (0.02); 80 mg (−0.4)* • Lips: PBO (0.02); 40 mg (−0.3)*; 80 mg (−0.6)* • Jaw: PBO (−0.1); 40 mg (−0.4); 80 mg (−0.6)* • Tongue: PBO (0.0); 40 mg (−0.5)*; 80 mg (−0.5)* • Upper extremities: PBO (0.1), 40 mg (−0.3)*; 80 mg (−0.4)* • Lower extremities: PBO (−0.1), 40 mg (−0.1), 80 mg (−0.3) • Trunk: PBO (0.1), 40 mg (−0.2)*; 80 mg (−0.3)*	Cohen's *d* effect sizes at Week 6 • Face: 40 mg (0.1); 80 mg (0.6) • Lips: 40 mg (0.4); 80 mg (0.7) • Jaw: 40 mg (0.3); 80 mg (0.6) • Tongue: 40 mg (0.5); 80 mg (0.5) • Upper extremities: 40 mg (0.5); 80 mg (0.7) • Lower extremities: 40 mg (0.02); 80 mg (0.2) • Trunk: 40 mg (0.4); 80 mg (0.5)
Meeting ≥50% AIMS response threshold at Week 6 • PBO (9%); 40 mg (24%)*; 80 mg (40%)*	NNTs at Week 6 • 40 mg (7); 80 mg (4)
Shift from AIMS item score ≥3 at baseline to ≤2 at Week 6[a] • Face: PBO (17%); 40 mg (50%); 80 mg (33%) • Lips: PBO (46%); 40 mg (73%); 80 mg (100%)* • Jaw: PBO (46%); 40 mg (77%)*; 80 mg (86%)* • Tongue: PBO (16%); 40 mg (55%)*; 80 mg (61%)* • Upper extremities: PBO (71%), 40 mg (50%); 80 mg (100%) • Lower extremities: PBO (67%), 40 mg (67%), 80 mg (88%) • Trunk: PBO (29%), 40 mg (80%)*; 80 mg (55%)	NNTs at Week 6[b] • Face: 40 mg (3); 80 mg (6) • Lips: 40 mg (4); 80 mg (2) • Jaw: 40 mg (4); 80 mg (3) • Tongue: 40 mg (3); 80 mg (3) • Upper extremities: 40 mg (−4); 80 mg (4) • Lower extremities: 40 mg (NE); 80 mg (5) • Trunk: 40 mg (2); 80 mg (4)
AIM-TD study results (deutetrabenazine)[14]	**Corresponding post hoc analysis[42]**
LSM CFB in AIMS total score at Week 12 • PBO (−1.4); 12 mg (−2.1); 24 mg (−3.2)*; 36 mg (−3.3)*	Cohen's *d* effect sizes at Week 12 • 12 mg (0.2); 24 mg (0.6); 36 mg (0.6)
Meeting ≥50% AIMS response threshold at Week 12 • PBO (12%); 12 mg (13%); 24 mg (35%)*; 36 mg (33%)*	NNTs at Week 12 • 12 mg (80); 24 mg (5); 36 mg (5)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CFB, change from baseline; LSM, least squares mean; NNT, number needed to treat; PBO, placebo.
*$p < 0.05$ versus placebo.
[a]AIMS item score ratings: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe.
[b]Negative NNT indicates better outcome with placebo. NNTs were not estimable if the same result was found for valbenazine and placebo.

of 5 was found for both statistically significant doses (12 and 18 mg BID) at Week 12.[42]

NNTs versus placebo for valbenazine have also been presented for AIMS item shift analyses, defined as shifting from an AIMS item score ≥3 (moderate or severe) at baseline to a score ≤2 (mild to none) at Week 6.[41] For valbenazine 80 mg, NNTs of 6 or lower were found in all 7 body regions (Table 2).

AIMS MCID or MCIC

AIMS data were pooled from DBPC trials to estimate the MCID for valbenazine and MCIC for deutetrabenazine.[44,45] The AIMS MCID for valbenazine was based on the mean change from baseline in AIMS total score in all study participants from KINECT, KINECT 2, and KINECT 3, regardless of treatment (valbenazine or placebo), who had global ratings of "minimally improved" or better (score ≤3) per CGI-TD (clinician impression) or PGIC (patient self-report). The AIMS MCIC for deutetrabenazine was based on the mean change from baseline in AIMS total score in participants from ARM-TD and AIM-TD who were treated with deutetrabenazine and had a global rating of "minimally improved" (score = 3) per clinician impression (CGIC) or patient self-report (PGIC).

For both VMAT2 inhibitors, a 2-point decrease in AIMS total score was found to represent a clinically meaningful improvement in TD severity, with 3–4 points considered a more robust improvement threshold.[44,45] Mean improvements in AIMS dyskinesia total scores were clinically meaningful for both medications.

Subgroup analyses

Post hoc analyses have shown that both valbenazine and deutetrabenazine are effective in various subgroups of clinical interest. Valbenazine was evaluated in older patients (age ≥55 years),[46] elderly patients (age ≥65 years),[47,48] and patients with schizophrenia/schizoaffective disorder or a mood disorder.[49,50] Deutetrabenazine was evaluated in older patients (≥55 years),[51] patients with schizophrenia/schizoaffective disorder or a mood disorder,[52] and regardless of concomitant antipsychotic use.[52]

Long-term studies

The long-term studies with valbenazine and deutetrabenazine did not include placebo arms, but results indicated that patients experience continued improvement in TD symptoms over time with both VMAT2 inhibitors. Importantly, no new safety signals were found in the long-term trials of either medication.

Valbenazine

The long-term studies for valbenazine included KINECT Extension (open label),[9] KINECT 3 Extension (with double-blind dosing, but no placebo),[15] J-KINECT Extension (Japanese study with double-blind dosing, but no placebo),[12] KINECT 4 (open label),[16] and Study 1506 (open-label roll-over).[17] Results from these studies indicated ongoing TD improvements in patients who received up to 48 weeks of valbenazine treatment (Supplementary Table S8).

KINECT 4 was designed to be more reflective of real-world use. The primary objective of this study was to evaluate the long-term safety of valbenazine. Participants who had a CGI-TD score ≤2 ("much improved" or "very much improved") at the end of Week 4 continued on 40 mg daily, whereas those who did not had their daily dose increased to 80 mg. The most common treatment-emergent adverse events (TEAEs) from Week 4 (end of initial treatment with 40 mg) to Week 48 (end of treatment with 40 or 80 mg) were urinary tract infection (8.5%) and headache (5.2%). Evaluations based on Columbia-Suicide Severity Rating Scale (C-SSRS) scores indicated that 5 participants had nonactive suicidal ideation at baseline (score 1–3), none of whom experienced worsening of suicidal ideation during valbenazine treatment; no suicidal behaviors (C-SSRS score 6–10) were reported. Psychiatric status remained stable, and no notable changes in vital signs, electrocardiograms (ECGs), or clinical laboratory tests were observed.

As part of the open-label design, AIMS scoring was based on assessments of movement severity by study investigators, rather than by blinded central video raters (as used in the DBPC trials). At Week 48, mean changes from baseline in AIMS total score were −10.2 and −11.0 with valbenazine 40 mg and 80 mg, respectively (Figure 3). These mean score changes were supported by the percentage of participants who met the following response thresholds at Week 48 (40 mg, 80 mg): AIMS ≥50% improvement (90.0%, 89.2%); CGI-TD score ≤2, defined as rating of "much improved" or "very much improved" (90.0%; 95.9%); and PGIC score ≤2 (90.0%, 89.2%) (Figures 3 and 4).

All individuals who completed a DBPC or long-term clinical trial were eligible to enroll in Study 1506, which was designed to provide additional long-term safety data in patients who wanted to continue taking valbenazine until it became available commercially.[17] Including participants' treatment in prior studies and in Study 1506, the mean total duration of valbenazine exposure was 19.7 months (range, 9.9–26.9 months). All participants were required to undergo a valbenazine washout before starting open-label treatment in this study, which included a 4-week initiation period with valbenazine 40 mg. After Week 4, the most common TEAEs were back pain (4.5%) and urinary tract infection (4.5%), as reported in 157 participants who had up to 60 weeks of valbenazine treatment in this study. The individuals who enrolled in this study presumably did so because of a positive experience with valbenazine in a previous study, which should be considered when interpreting study results. Notably, however, approximately 98% of participants expressed satisfaction with valbenazine before starting this study and by the end of the study, which was stopped when valbenazine became commercially available.

Deutetrabenazine

Participants who completed the ARM-TD and AIM-TD trials were eligible to continue in the long-term extension study (RIM-TD), with reported results at Week 106[18] and Week 145[19] (Supplementary Table S8). Evaluation of long-term safety and tolerability was the primary objective of this study, and adverse events (AEs) were presented as exposure-adjusted incidence rates (EAIRs) with no breakdown by dose. At Week 145, the mean daily dose of deutetrabenazine was 39.4 mg. Among participants in the Week 145 analysis (N = 337), the most common AEs were anxiety (EAIR = 0.07, n = 42 [12.5%]), somnolence (EAIR = 0.05, n = 34 [10.1%]), and depression (EAIR = 0.005, n = 33 [8.9%]).[19] No notable changes were observed in safety scales that measured akathisia, anxiety, depression, sleepiness, and cognitive impairment.

In participants who reached the Week 145 visit, the mean change from baseline in AIMS total score was −6.6 (Figure 3).[19] This outcome was supported by the percentage of participants who

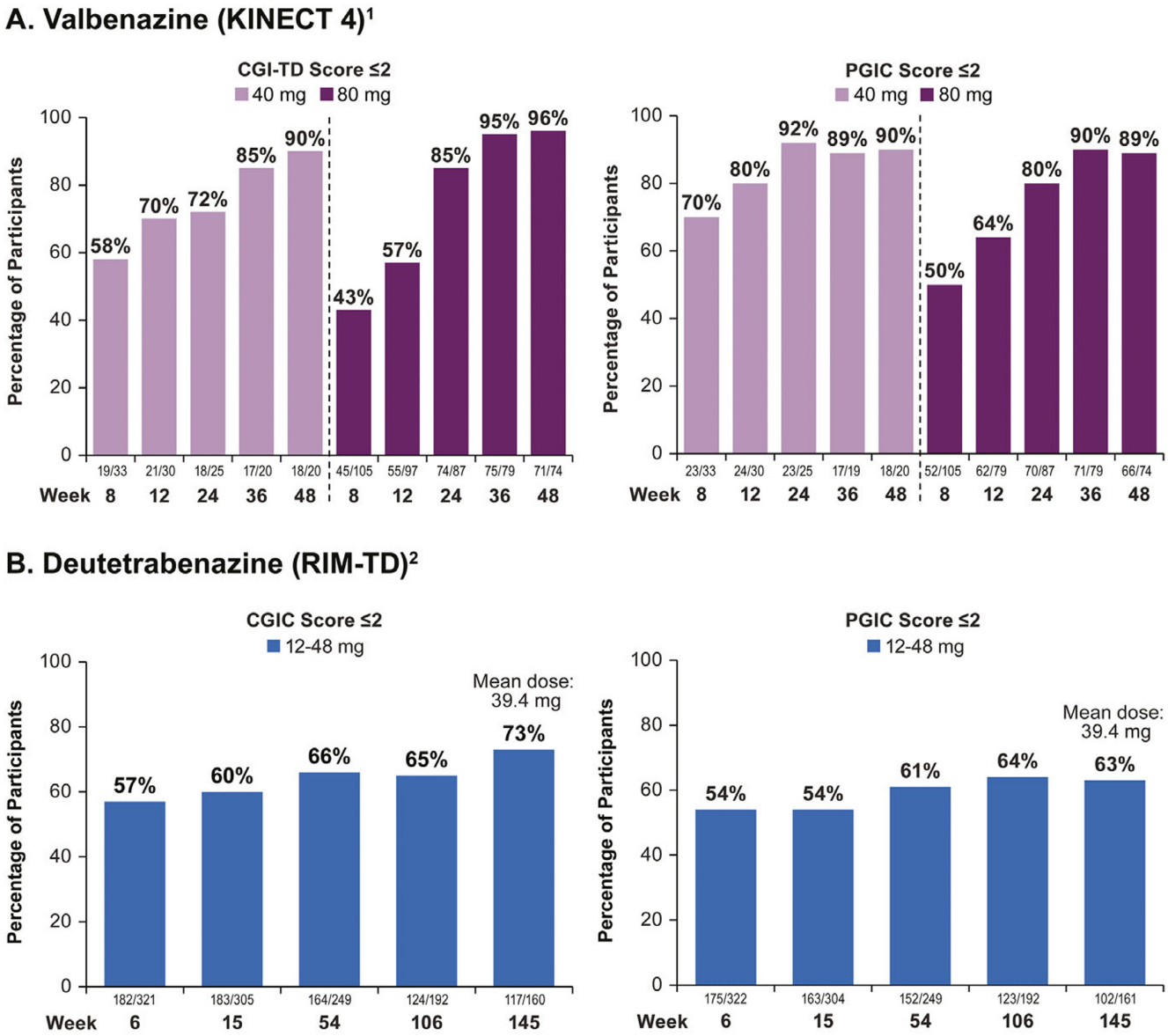

Figure 4. Global improvement outcomes in long-term studies. Global improvements in TD, as assessed by study investigators (CGI-TD, CGIC) and self-reported by study participants (PGIC), are presented. (A) In the 48-week open-label KINECT 4 study, approximately 90-95% of participants met the threshold for CGI-TD and PGIC response, which were both defined as a score of 1 ("very much improved") or 2 ("much improved"). (B) The same response thresholds were used in the long-term open-label study with deutetrabenazine. At Week 145 in this study, 73% of participants had a CGIC score ≤2 and 63% had a PGIC score ≤2.
Abbreviations: CGIC, Clinical Global Impression of Change; CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; PGIC, Patient Global Impression of Change.
References: [1] Marder et al., *J Clin Psychopharmacol* 2019;39(6):620–7. [2] Hauser et al., *Front Neurol* 2022;13:773999.

met the following response thresholds at Week 145: AIMS ≥50% improvement (67%); CGIC score ≤2 (73%); PGIC score ≤2 (63%) (Figures 3 and 4).

Conclusions and future directions

TD has been estimated to affect approximately 20–30% of patients taking an antipsychotic, with higher risks associated with older age and cumulative exposure to antipsychotics, as well as female sex, bipolar/mood disorders, and use of older antipsychotics.[53–57] Prior to the approval of valbenazine and deutetrabenazine for TD in 2017, treatment options were limited. Tetrabenazine, which is approved for HD chorea, was used off label for TD, but this medication requires more frequent dosing than either valbenazine or deutetrabenazine and is associated with more adverse effects. Many other treatments have been evaluated for TD, but the evidence for these medications was limited at best. Anticholinergics, which are appropriate for drug-induced parkinsonism and acute dystonia, are not recommended for TD and may even worsen the symptoms of TD.[27,58] Valbenazine and deutetrabenazine have both been evaluated in multiple well-controlled clinical trials and the supporting evidence for these medications is strong.[24,59,60] Efficacy results from pivotal trials for each medication differed, but trends of TD severity reduction in long-term studies suggest that patients can expect ongoing improvement with both drugs beyond the time frames of their respective studies.

The primary objective of this review article is to present the body of evidence for both valbenazine and deutetrabenazine, while also

highlighting the new formulations and doses that were later approved. Valbenazine now includes a once-daily 60-mg dose and a sprinkle formulation that can be mixed into soft foods,[1] which may be useful for patients who have difficulty swallowing or pill aversion, or who simply prefer such a formulation. Deutetrabenazine now includes a once-daily formulation,[2] which can help with pill burden for prescribers and patients.

Although both medications are VMAT2 inhibitors that have been shown to be safe and highly effective in TD, they are pharmacologically different with their own pharmacokinetic and pharmacodynamic profiles. Therefore, if a patient is experiencing poor tolerability and/or treatment response with one medication, switching to the other medication could be considered. Advanced age, along with comorbid conditions and concomitant medications that affect drug metabolism or clearance, might also need to be considered when discussing TD treatment options with patients. More research with both medications would be needed to understand whether they have differential effects on the types of movements associated with TD (eg, stereotypic, choreiform), but current data suggest efficacy in all TD phenomenology. Most importantly, all patients taking an antipsychotic or other DRBAs should be regularly assessed for abnormal movements.[61] Once detected, understanding and identifying the phenomenological differences between TD and other drug-induced movement disorders (eg, parkinsonism, acute dystonia, akathisia) is crucial to achieving successful treatment outcomes.[62]

The impact of TD is substantial, and the effects of patients' symptoms on their physical functioning, ability to work or attend school, social engagement, and emotional well-being cannot be overlooked.[63–67] The importance of recognizing the impact of TD is evidenced by development of the following scales: IMPACT-TD, a clinician-rated assessment developed using a modified Delphi process; Clinician's Tardive Inventory (CTI), a validated clinician-rated assessment that has demonstrated strong interrater and test–retest reliability; and Tardive Dyskinesia Impact Scale (TDIS), which is the only psychometrically validated patient-reported assessment for TD.[68–71] With these scales and other measures, future studies that evaluate the effects of treatment on patient functioning and the quality of life are expected.

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Data availability. All data included in this review are available in the published studies cited herein. No new datasets were generated or analyzed for this review.

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